UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Note to Reader

Background: As part of its effort to involve the public in the implementation of the Food Quality Protection Act of 1996 (FQPA), which is designed to ensure that the United States continues to have the safest and most abundant food supply. EPA is undertaking an effort to open public dockets on the organophosphate pesticides. These dockets will make available to all interested parties documents that were developed as part of the U.S. Environmental Protection Agency's process for making reregistration eligibility decisions and tolerance reassessments consistent with FQPA. The dockets include preliminary health assessments and, where available, ecological risk assessments conducted by EPA, rebuttals or corrections to the risk assessments submitted by chemical registrants, and the Agency's response to the registrants' submissions.

The analyses contained in this docket are preliminary in nature and represent the information available to EPA at the time they were prepared. Additional information may have been submitted to EPA which has not yet been incorporated into these analyses, and registrants or others may be developing relevant information. It's common and appropriate that new information and analyses will be used to revise and refine the evaluations contained in these dockets to make them more comprehensive and realistic. The Agency cautions against premature conclusions based on these preliminary assessments and against any use of information contained in these documents out of their full context. Throughout this process, If unacceptable risks are identified, EPA will act to reduce or eliminate the risks.

There is a 60 day comment period in which the public and all interested parties are invited to submit comments on the information in this docket. Comments should directly relate to this organophosphate and to the information and issues available in the information docket. Once the comment period closes, EPA will review all comments and revise the risk assessments, as necessary.

These preliminary risk assessments represent an early stage in the process by which EPA is evaluating the regulatory requirements applicable to existing pesticides. Through this opportunity for notice and comment, the Agency hopes to advance the openness and scientific soundness underpinning its decisions. This process is designed to assure that America continues to enjoy the safest and most abundant food supply. Through implementation of EPA's tolerance reassessment program under the Food Quality Protection Act, the food supply will become even safer. Leading health experts recommend that all people eat a wide variety of foods, including at least five servings of fruits and vegetables a day.

Note: This sheet is provided to help the reader understand how refined and developed the pesticide file is as of the date prepared, what if any changes have occurred recently, and what new information, if any, is expected to be included in the analysis before decisions are made. **It is not meant to be a summary of all current information regarding the chemical.** Rather, the sheet provides some context to better understand the substantive material in the docket (RED chapters, registrant rebuttals, Agency responses to rebuttals, etc.) for this pesticide.

Further, in some cases, differences may be noted between the RED chapters and the Agency's comprehensive reports on the hazard identification information and safety factors for all organophosphates. In these cases, information in the comprehensive reports is the most current and will, barring the submission of more data that the Agency finds useful, be used in the risk assessments.

Jack E. Housenger, Acting Director
Special Review and Reregistration Division

MEMORANDUM

SUBJECT: Diazinon: Toxicology Chapter for the RED as revised 3/30/00 in response to the Novartis Crop Protection, Inc. responses submitted February 9, 2000 to the RED.

TOX CHEM No.: 342
CAS No.: 333-41-5
PC No.: 057801
Barcode No.: D238960
Submission No.: S528166
ReRegistration Case No.: 0238

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Attached is the toxicology chapter for the Registration Eligibility Decision (RED) document for diazinon. This document is available on a computer disk.

Human Health Assessment

The toxicology data base for diazinon is sufficient to support the ReRegistration Eligibility Decision (RED).

The following data gaps are indicated at this time.

Series 870.6300. Developmental Neurotoxicity.

1. Toxicology Assessment

A. **Acute Toxicity** - Revised March 30, 1000 from the original HED Toxicology Chapter.

Table 1 below summarizes the acute toxicity of diazinon. These studies are discussed as follows:

Table 1. Summary of acute toxicity of technical Diazinon.

Study	Results	Toxicity Category
81-1. Acute Oral-rats. MRID No.: 41407218.	LD_{50} = 1340 (1140-1610)mg/kg ♂ = 1160 (999-1350) mg/kg ♀ = 1250 (1080-1415) mg/kg combined sexes (95% confidence limits)	III
81-2. Acute Dermal -rabbits. MRID No.: 41407219.	LD_{50} > 2020 mg/kg ♀/♀	III
81-3. Acute Inhalation - rats. MRID No.: 41407220.	LC_{50} = > 2.33 mg/L (four hour exposure with a MMAD of 2.046 μm.	III
81-4. Primary Ocular Irritation - rabbits. MRID No.: 41407221.	Minimally irritating.	III
81-5. Primary Dermal Irritation - rabbits. MRID No.: 41407222.	maximum irritation score 2.8 (slight irritant)	III
81-6. Dermal Sensitization - guinea pigs. MRID No.: 41407223 and 00232008	Not a sensitizer in guinea pig (Buehler assay). [Human study indicates 5-6/56 showed positive sensitization].	--
81-7. Delayed type neurotoxicity-hens. MRID No.: 44132701	No evidence of delayed type neurotoxicity at 100 mg/kg, a dose > than the LD_{50}; protected by atropine and physostigmine.	--

Note: The studies selected for inclusion in Table I were from one set of acute studies with the

technical grade of diazinon provided by the Ciba-Geigy Corporation (now Novartis Crop Protection, Inc.) and replace the data set provided by the Nippon-Kayaku Company that was presented in the original toxicology chapter for the diazinon RED.

81-1. Acute oral toxicity-rats (1989).

Three groups of 5/sex HSD:(SD) BR strain young adult rats (fasted) were dosed with either 800, 1200 or 2o50 mg/kg of diazinon (technical grade Diazinon MG8, Ciba-Geigy Co.) undiluted and observed for 14 days in an acute oral toxicity assessment (MRID NO.: 41407218).

The following LD_{50}s were determined:

LD_{50} = 1350 (1140-1610) mg/kg ♂
= 1160 (999-1350) mg/kg ♀
= 1250 (1080-1450) mg/kg combined.

which places this material in Toxicity Category III. A variety of 21 listed symptoms including tremors, hunched appearance, green urine staining, rough coat, soft feces, ataxia, gasping, salivation, depression, corneal opacity, constricted pupils and Chromodacryorrhea as well as others resulted. Some symptoms persisted to day 4. Necropsy was unremarkable for the survivors. The rats that died due to treatment displayed some of the same conditions as noted in clinical signs plus reduced content of the gastro intestinal tract and for discoloration in the content. There was a body weight loss.

This study is classified as ACCEPTABLE and satisfies the requirement for a series 81-1 acute oral toxicity study.

81-2. Acute dermal toxicity-rabbits (1989).

A single group of 5/sex New Zealand White rabbits were dosed with 2020 mg/kg of diazinon (Diazinon MG8 87.7% technical grade, Ciba-Geigy) applied directly to the prepared backs and kept in place for 24 hours (MRID NO.: 41407219).

Two of the five females died on day 3 postdosing; none of the males died. The LD_{50} for males and females is > 2020 mg/kg. Diazinon is classified as Toxicity Category III. Transient symptoms (up to day 6) included no or decreased defecation, diarrhea, and nasal discharge and in females tremors and salivation. Necropsy revealed in the decedents g-I tract distended with gas and discoloration the contents of the stomach.

The study was not considered acceptable for both males and females because although there were deaths at the limit dose a condition may require additional testing to determine the LD_{50}. Additional dermal toxicity testing is not being requested.

81-3. Acute inhalation toxicity-rats (1989).

Three groups of 5/sex Sprague-Dawley strain rats were exposed to an atmosphere containing 2.33 mg/L (analytically determined concentrations of diazinon from Diazinon MG8, 87.7% purity, Ciba-Geigy) for 4 hours by whole body exposure. The mass median aerodynamic diameter was reported to range from 1.97 to 2.56 microns with geometric standard deviations of

1.77 to 1.96. The test atmosphere was generated by a metering pump and mixing with air. The rats were observed for 14 days. MRID No.: 41407220.

The following LC_{50}s were determined:

LC_{50} > 2.33 mg/L for a four hour exposure.

to place this product in Toxicity Category IV by the inhalation route. There were no deaths. The symptoms included piloerection, activity decrease, ptosis, nasal discharge and salivation and polyuria. Some symptoms persisted until day 3. Necropsy was unremarkable. There was no affect on body weight reported.

This study is classified as ACCEPTABLE satisfies the requirement for a series 81-3 acute inhalation toxicity study.

81-4. Primary ocular irritation-rabbits (1989).

The eyes of nine adult (3 males and 6 females) rabbits (New Zealand White) were instilled with 0.1 mL of diazinon (Diazinon MG8 87.7%, Ciba-Geigy) and after 30 seconds the eyes of three rabbits were washed with deionized water. then examined for reactions at 1, 24, 48 and 72 hours after instillation. MRID No.: 41407221.

No corneal involvement resulted. There was some transient conjunctival irritation and the average irritation scores after one hour were 9 for the non washed and 5.3 for the washed animals. The test material was thus considered minimally irritating or Toxicity Category III.

This study is classified as ACCEPTABLE and satisfies the requirement for a series 81-4 ocular toxicity in rabbits.

81-5. Primary dermal irritation-rats (1989).

The backs of six rabbits (New Zealand White) were prepared by clipping but not abrading and a dose of 0.5 mL of diazinon (Diazinon MG8 87.7% purity, Ciba-Geigy) was applied and kept in place by occlusive bandages for four hours. MRID No.: 41407222.

A maximum primary irritation score of 2.8 was determined. Sufficient data were generated to classify the test material as a slight irritant Toxicity Category III.

This study is classified as ACCEPTABLE and satisfies the requirement for a series 81-5 dermal irritation study in rabbits.

81-6. Dermal sensitization-guinea pigs (1989).

<u>Guinea pig study.</u>

In a modified Buehler study (MRID NO.: 41407223), a single group of 10 (male) guinea pigs were first induced by application of 0.5 mL of neat diazinon (Diazinon 87.7% technical grade, Ciba-Geigy) to the prepared backs three times or on days 1, 3 and 6 and 0.5 mL of 10% v/v solution of diazinon in ethanol were applied on days 8, 10, 13, 15, 17, 20, 22 and 36. The

dose was reduced from neat diazinon to the 10% dilution because the neat preparation was lethal to one animal. After a two week rest the guinea pigs were challenged.

No erythema or edema was reported to develop in response to the challenge dose. Thus, the test material was not shown to be a sensitizer in this modified Buehler assay in guinea pigs.

This study is classified as ACCEPTABLE and satisfies the requirement for a series 81-6 dermal sensitization study.

Human study with volunteers.

In a special study with human volunteers (MRID No.: 00232008) a group of 56 human volunteers were induced and later challenged with diazinon technical (1% emulsified in water with Tween 80) or diazinon formulation 2E emulsion diluted with water. Induction consisted a series of 9 applications made over 2-3 day intervals of 0.5 mL of test material applied using a Warbil patch and kept in place on the upper arm for 24 hours. The challenge application was made 14 days after the last induction application.

The study authors conclusion was that in six of the 56 volunteers diazinon induced a fairly persistent sensitization. The subjects were retested in second and third trials and positive responses were also obtained. **Diazinon is considered a positive dermal sensitizer in humans.**

81-7. Acute delayed type neurotoxicity-hens (1996).

Five groups of hens (LSL-Lohman) were dosed as control, 10, 30, 100 mg/kg of diazinon (96.3% a.i.) in peanut oil or 500 mg/kg of TOCP (a positive control). There were 12 hens/group except 20/group for the 100 mg/kg diazinon dose group. Diazinon was administered by gavage and the hens were protected from acute poisoning by a vigorous application of atropine (20 mg/kg) plus physostigmine (0.15 mg/kg) or atropine alone both intramuscularly. Six hens/group were assessed for clinical signs, ataxia and for histopathological changes in the brain, spinal cord and peripheral nerves after 21 days. Three hens/group were sacrificed after 24 and 48 hours for biochemical investigations (ChE/AChE and neurotoxic esterase effects). MRID No.: 44132701).

At 10 mg/kg and above transient symptoms including reduced activity (6/6 hens) and impaired gait (5/6 hens) were noted. Diarrhea, salivation and recumbency were also noted at 30 or 100 mg/kg. One hen at 30 mg/kg and three hens at 100 mg/kg died in spite of the vigorous treatment with atropine and physostigmine. No evidence of delayed type neuropathology was apparent in the diazinon treated hens.

Plasma ChE was inhibited at 10 mg/kg (93% and 97% at 24 and 48 hours). Brain AChE was inhibited 64% and 29% at 24 and 48 hours at 30 mg/kg and 83% and 66% at 100 mg/kg. RBC AChE was inhibited to only 15% at 100 mg/kg diazinon at 24 hours only.

The TOCP positive control group resulted in the expected positive response of ataxia after two weeks associated with histopathological changes in the cerebellum and spinal cord. **Diazinon was not demonstrated to induce delayed type neuropathology in hens at**

dose levels up to and including 100 mg/kg in hens protected with atropine and physostigmine.

This acute delayed neurotoxicity study in hens is classified as ACCEPTABLE. This study satisfies the guideline requirement for an acute neurotoxicity assessment in hens (81-7).

B. **Subchronic toxicity.**

81-1a/b. Subchronic oral toxicity rodent(a)/nonrodent(b).

Rodent Studies.

Study 1 (1991). In this special subchronic feeding study (MRID No.: 41886301) 7 groups of 30/sex Sprague-Dawley strain rats were dosed as 0, 0.2, 0.5, 2.0, 20, 100 or 300 ppm of diazinon (Nippon Kayaku technical grade, 87.84% purity) corresponding to 0.02, 0.05, 0.2, 2, 9.5 and 28 mg/kg/day for 42 days. 10/sex were sacrificed and assessed for plasma CHE, RBC AChE and brain AChE at days 14, 28 and 42.

No systemic toxicity was evident.

Plasma ChE was inhibited at 2 ppm in females (32-53%) and at 20 ppm in males (38-41%). RBC AChE was inhibited at 20 ppm in males (46-55%) and females (50-61%). Brain AChE was inhibited at 100 ppm in females (35%) and at 300 ppm in males (14%). **The LOEL is 2 ppm (0.2 mg/kg/day) based on plasma ChE inhibition in females. The NOEL is 0.5 ppm (0.05 mg/kg/day).**

The study was classified as SUPPLEMENTARY but is acceptable for the stated purpose.

Study 2 (1989). In this special subchronic study (MRID Nos.: 41432301 and 41649401), 7 groups of 10/sex Sprague-Dawley strain rats were dosed as 0, 0.2, 0.5, 2, 20, 100 or 300 ppm diazinon for 42 days. Both old and new manufacturing lots were compared. These dose levels corresponded to 0.02/0.02, 0.04/0.05, 0.17/0.19, 1.68/1.82, 8.60/9.27 or 25.8/29 mg/kg/day for the newer manufacturing process of diazinon for males/females.

No systemic effects were reported. **The LOEL for systemic effects is > 29 mg/kg/day. The NOEL is $\geq$ 29 mg/kg/day.**

Plasma ChE was inhibited at 0.2 ppm in females (18%, $p < 0.05$) at least at study termination; at 0.5 ppm, it was inhibited in males (12%, $p < 0.01$) and females (17%, $p < 0.05$); and at 2 ppm it was inhibited in males up to 13% and in females up to 49%. RBC AChE was inhibited at 20 ppm in males (29-35% range for different assay intervals) and in females (16-35%). Brain AChE was inhibited at 100 ppm in males (13%) and at 300 ppm in females (55%). At 300 ppm males were inhibited 29%. **The LOEL is 2 ppm (0.19 mg/kg/day) based on plasma ChE inhibition in females. The NOEL is 0.5 ppm (0.05 mg/kg/day).**

This study is classified as SUPPLEMENTARY.

Study 3 (1988). In a feeding study (MRID No.: 40815003), 5 groups of 10/sex Sprague-Dawley strain rats were dosed with 0, 0.5, 2, 100 or 1000/2000/4000 ppm diazinon MG-8 for six weeks. These dose levels correspond to 0.04/0.05, 0.2/0.2, 8.4/9.4 and 165/198 mg/kg/day of diazinon for males/females.

Systemic toxicity was evident in the 165/198 mg/kg/day dose group only and consisted of soft feces, decreased body weight gain (4-19% in males and 6-9% in females), decreased feed consumption. **The LOEL for systemic toxicity is 165 mg/kg/day based on decreased body weight. The NOEL is 9.4 mg/kg/day.**

Plasma ChE was inhibited at 2 ppm in females (~35%, $p < 0.01$) and males (~18%, not significant). At 100 ppm, RBC AChE was inhibited in males (~21%, $p < 0.01$) and females (21%, $p < 0.01$) and brain AChE was inhibited (females 24%, $p < 0.05$). **The LOEL is 0.2 mg/kg/day based on inhibition of plasma ChE. The NOEL is 0.05 mg/kg/day.**

The study is classified as SUPPLEMENTARY.

Study 4 (1988). In a subchronic feeding study, 5 groups of 15/sex Sprague-Dawley strain rats were dosed as 0, 0.5, 5, 250 or 2500 ppm of diazinon MG-8 for 13 weeks (MRID No.: 40815003). These doses correspond to 0.03/0.04, 0.3/0.4, 15/19 or 168/212 mg/kg/day of diazinon in male/female rats. Systemic toxicity was evident in the 2500 ppm dose group only and consisted of hypersensitivity to sound and touch, aggressiveness, deceased body weight gains, decreased feed consumption, deceased hemoglobin and hematocrit, increase liver weight (absolute and relative), hepatocellular hypertrophy. **The LOEL for systemic effects is 168 mg/kg/day based on several parameters including decreased body weight. The NOEL is 19 mg/kg/day.**

Plasma ChE was inhibited at 5 ppm in males (26%) and females (78%, both $p < 0.01$) and RBC AChE was inhibited in females (17%, $p < 0.01$). At 250 ppm, RBC AChE was inhibited in males (27%, $p < 0.01$) and brain AChE was inhibited in females (41%, $p < 0.01$). At 2500 ppm brain AChE was inhibited in males (49%) and females (57%). **The LOEL is 0.3 mg/kg/day based on plasma ChE and RBC AChE inhibition. The NOEL is 0.04 mg/kg/day.**

This study is classified as GUIDELINE and satisfies the requirement for a series 82-1a subchronic feeding study in rats.

Dog Studies.

Study 1 (1988). In a four week subchronic pilot study with dogs (MRID No.: 40815004), five groups of 4/sex beagle dogs were dosed with diets containing 0, 0.5, 2, 20 or 500 ppm diazinon (MG-8) for four weeks. These dose levels corresponded to 0.02/0.023, 0.073/0.082, 0.80/0.75 or 14.68/15.99 mg/kg/day for males/females.

Systemic toxicity was evident at 500 ppm only and included emesis and decreased body weight and feed consumption. **The LOEL for systemic toxicity is 14.68 mg/kg/day based on body weight effects. The NOEL is 0.80 mg/kg/day.**

Plasma ChE was inhibited at 0.5 ppm in females (~29%, $p < 0.01$) and in males (~8%, not

significant). Only at 500 ppm was RBC (26-39% in both males and females) and brain (44% in males, 50% in females) AChE inhibited (all $p < 0.01$). **The LOEL is < 0.023 mg/kg/day based on plasma ChE inhibition. The NOEL was not determined.**

This study is classified as SUPPLEMENTARY.

Study 2 (1988). In a 90 day study in dogs (MRID No.: 40815004), 5 groups of 4/sex beagle dogs were dosed with diazinon (MG-8) at dose levels of 0, 0.1, 0.5, 150 or 300 ppm for 13 weeks. These doses correspond to 0.0034/0.0037, 0.020/0.021, 5.9/5.6 or 10.9/11.6 mg/kg/day for males/females.

Systemic effects were noted at 150 ppm and included decreased body weight gain in females (34%, not significant), total protein (~1.4%) and calcium (~5%). At 300 ppm, both male and female body weight gain was decreased (33% males and 45% females), and decreased food consumption and total protein and calcium deceases were increased. **The systemic LOEL is 5.6 mg/kg/day based on deceased body weight. The NOEL is 0.021 mg/kg/day.**

Plasma ChE was inhibited in females at 0.5 ppm (~16%, not significant) and in males ~30% ($p < 0.05$). At 150 ppm, plasma ChE was inhibited about 80% in both males and females. At 150 ppm RBC (~25% in males and ~31% in females, $p < 0.01$) and brain AChE (31% in males and 30% in females) were inhibited. At 300 ppm, brain AChE was inhibited ~42% in males and ~45% in females. **The LOEL was 0.020 mg/kg/day based on plasma ChE inhibition in males. The NOEL was 0.0037 mg/kg/day.**

This study is classified as SUPPLEMENTARY and does not satisfy the requirement for a series 81-2b subchronic feeding study in a non-rodent species. This requirement has been met by the dog chronic feeding study (see below) for series 81-3b.

<u>Human Study (1966).</u>

In a special study with humans (MRID No.: 00091536, males only), groups of 3 volunteers were dosed with 0.02 or 0.025 mg/kg/day of diazinon (a.i. from Diazinon 50WP) in corn starch by capsule for 38 or 43 days. A control group of 3 was dosed with corn starch only. Frequent assessments (every 2-3 days) of the blood for plasma CHE and RBC AChE were made.

All three volunteers showed inhibition (8-38%) in the 0.025 mg/kg/day dose group. Although two of the three volunteers dosed with 0.02 mg/kg/day showed consistent depression (9-30%) of plasma ChE relative to their pretest values, a definite conclusion of significant plasma ChE inhibition could not be established. RBC AChE was not inhibited. **The LOEL is 0.025 mg/kg/day based on plasma ChE inhibition. The NOEL is 0.02 mg/kg/day.**

This special study in humans is classified UNACCEPTABLE (Non-Guideline).

82-2. 21-day dermal toxicity studies (1984).

In a dermal toxicity study with rabbits (MRID No.: 40660807), 4 groups of 5/sex New Zealand White rabbits were dosed as control, 1, 5 or 100/50 mg/kg/day of diazinon for five days/week for three weeks. The initial dose of 100 mg/kg/day was lethal (4/5 males) and reduced to 50 mg/kg/day after 7 days. The test material (technical diazinon) was applied as a suspension in polyethylene glycol 300, covered and kept in place for 6 hours. The rabbits were assessed for clinical signs and at day 21 were sacrificed and necropsied and subjected to hematology and clinical chemistry including plasma ChE and RBC and brain AChE assessments.

No symptoms were noted in the high dose group when the dose was reduced to 50 mg/kg/day. **The LOEL is 100 mg/kg/day based on deaths. The NOEL is 50 mg/kg/day.**

Plasma ChE was inhibited ($p < 0.05$ or less) at termination at all dose levels in females with there being 32%, 35% and 62% inhibition at 1, 5 and 50 mg/kg/day. At 5 mg/kg brain AChE was inhibited 18% in females but not in males. At 50 mg/kg, brain AChE was inhibited 28% in males (one animal) and 43% in females. RBC AChE was statistically inhibited at 50 mg/kg/day in males (39%, based on one male) and females (32%). **The LOEL is < 1 mg/kg/day based on plasma ChE inhibition. The NOEL was not established.**

This subchronic dermal toxicity study in rabbits has been classified as ACCEPTABLE and satisfies the requirement for a series 82-3 subchronic dermal toxicity study.

82-4. 21-day inhalation study- rats (1988).

In a 21-day inhalation study (MRID No.: 40815002), four groups of 15/sex Sprague-Dawley strain rats were dosed as control, 0.1, 1, 10 and 100 μg/L of diazinon MG-8 (87% purity) for six hour/day 7 days/week.

No symptoms were reported in response to treatment. **The LOEL is > 100 μg/L for systemic effects. The NOEL is 100 μg/L**

At 0.1 μg/L, plasma ChE was inhibited in males (30%, $p < 0.05$) and females (56%, $p < 0.05$). Progressively higher levels of inhibition were noted at higher doses. RBC AChE was inhibited in males (18%, $p < 0.05$) at 0.1 μg/L and inhibition was progressively greater at higher doses. In females RBC AChE was statistically inhibited (45%) at 1 $\mu\mu$g/L. At 1 μg/L brain AChE was inhibited in both males (13%, $p < 0.05$) and females (15%, $p < 0.05$). **The LOEL is < 0.1 μg/L based on plasma ChE in both sexes and RBC AChE in males. The NOEL was not determined.**

This study has been classified as ACCEPTABLE and to satisfy the requirement for a series 82-3 subchronic inhalation toxicity study in rats.

82-5. Subchronic neurotoxicity in hens .

No study available or required at this time.

C. **Chronic toxicity**.

83-1a Rat Study (1991).

In a chronic feeding study (MRID No.: 41942002) in rats, 6 groups of 30/sex Sprague-Dawley strain rats were dosed as 0 (two groups), 0.1, 1.5, 125 or 250 ppm diazinon MG-8 (87.7% purity) for 98 weeks. These dose levels correspond to 0.004/0.005, 0.06/0.07, 5/6 or 10/12 mg/kg/day for males/females. The control groups (both sets) and the 250 ppm dose group had satellite groups of 10/sex that were reserved for a 4 week recovery period following dosing for 52 weeks.

No systemic toxicity was evident. **The systemic LOEL is > 12 mg/kg/day. The NOEL is ≥ 12 mg/kg/day.**

Plasma ChE was inhibited at 1.5 ppm in females (58%, $p < 0.01$) and in males (51%, $p < 0.05$ at termination only). It was noted that at 0.1 ppm at some assay intervals, females were inhibited up to 26% and males up to 36% but statistical significance was not attained. At 125 ppm, RBC AChE was inhibited in males (28%, $p < 0.01$) and in females (26%, $p < 0.01$). Brain AChE was inhibited at 125 ppm for males (24%, $p < 0.01$) and females (29%, $p < 0.01$). **The LOEL is 0.06 mg/kg/day based on inhibition of plasma ChE. The NOEL is 0.005 mg/kg/day.**

This study has been classified as ACCEPTABLE and to satisfy the requirement for a series 83-1 chronic feeding study in rats.

83-1b. Non-rodent studies

1. Monkey Study (1966).

In a chronic toxicity study (MRID 00057664, 00064319 and 00064320), diazinon (formulated as 50WP, 48.6% purity) was administered by stomach tube to 3/sex rhesus monkeys (Maraca mulatto) at dose levels of 0, 0.05, 0.5 and 5 mg diazinon (a.i.)/ kg/day for week 6-101. For, the first five weeks of this 106 week study, each group received twice the above listed amount except the high dose which was not dosed on weeks 4-5. The initial dose levels were reduced by one half due to toxicity at 10 mg/kg/day. Four monkeys died of intercurrent infections not related to treatment.

At 10 mg/kg/day, effects were noted in assessments on clinical signs (appearance resembling dysentery in 2/6 monkeys, soft stools) and body weight decrease. After lowering the dose, soft stools were noted to be present in all treated groups without a dose response but the significance of soft stools at these doses is too indefinite to interpret. No effects on hematology, clinical chemistry, organ weight or histopathology were noted. **The LOEL for systemic effects is 10 mg/kg/day based on clinical signs. The NOEL is 5 mg/kg/day.**

When inhibition is expressed relative to the pretest group values, plasma ChE at 0.5 mg/kg/day was inhibited 18-90% in males and females. At 0.05 mg/kg/day plasma ChE was inhibited 10-36% in males, however, it was not considered a definite or biologically significant

decrease in activity. RBC AChE was inhibited at 0.5 mg/kg/day for males (~18%-44%) and for females (maximum 20%). **The LOEL is 0.5 mg/kg/day for plasma ChE and RBC AChE inhibition. The NOEL is = 0.05 mg/kg/day.**

This chronic toxicity study in the monkey is ACCEPTABLE (NONGUIDELINE) and does not satisfy the guideline requirement for a chronic oral study (83-1b) in a non-rodent species. Note: This study requirement has been satisfied with a dog study.

2. Dog Study (1991).

In a chronic feeding study with dogs (MRID No.: 41942001), five groups of 4/sex beagle dogs were dosed with 0, 0.1, 0.5, 150 or 300/225 ppm diazinon (MG-8) for 52 weeks. The high dose group was initiated at 300 ppm but was reduced after 14 weeks to 225 ppm. These dose levels corresponded to 0.0032/0.0037, 0.015/0.020, 4.7/4.5 or 7.7/9.1 mg/kg/day.

Systemic toxicity was evident at 150 ppm based on decreased body weight gain (up to 64%) and food consumption (up to 27%) particularly in males and increased serum amylase (24-59%). **The LOEL for systemic toxicity was 4.5 mg/kg/day based on body weight gain decrease. The NOEL is 0.02 mg/kg/day.**

At 0.5 ppm **plasma ChE** was inhibited in females 18-40% ($p < 0.01$). At 150 ppm **RBC AChE** was inhibited in males (25-34%, $p < 0.01$) and in females (26-33%, $p < 0.01$). Plasma ChE was inhibited at 0.1 ppm (9-28%, $p < 0.05$) in females and at 0.5 ppm 5-25% ($p < 0.05$) in males. **Brain AChE** was inhibited at 150 ppm in females (26%, $p < 0.05$) and males (15%, not significant). At 225/300 ppm, male brain inhibition reached 25% but was not significant while female brain inhibition reached 35% ($p < 0.05$). **The LOEL is 0.5 ppm (0.02 mg/kg/day) based on plasma ChE inhibition in females. The NOEL = 0.1 ppm (0.0037 mg/kg/day).**

This chronic feeding study in dogs is classified as ACCEPTABLE and satisfies the guideline requirement for a series 82-1b chronic feeding study in a non-rodent species.

D. **Carcinogenicity**.

83-2a Rat carcinogenicity study.

In a carcinogenicity toxicity study (MRID 00073372),diazinon (98% purity) was administered to groups of Fischer 344 (50/sex) rats at either 400 or 800 ppm (estimated to be 20 and 40 mg/kg/day) for 103 weeks. The control group consisted of 25/sex untreated rats.

No systemic effects were reported. The study itself did not provide a basis for concluding that adequate doses were assessed. The dose levels tested are well established from other studies to be moderately strong inhibitors of plasma ChE, RBC AChE and brain AChE. No evidence of compound related tumors was apparent in this study. **The LOEL for systemic effects is > 40 mg/kg/day.**

At the doses tested, there were no treatment related increases in tumor incidence when compared to controls. Dosing was considered adequate based on the known property of diazinon to be a moderate inhibitor of ChE/AChE in several other studies at the dose levels tested.

This carcinogenicity study in the rats is ACCEPTABLE and satisfies the guideline requirement for a carcinogenicity study (83-2(a) in rats.

83-2b. Mouse studies (1979).

In a carcinogenicity toxicity study (MRID 00073372) diazinon (98% purity) was administered to 50/sex B63CF1 strain mice in their diets at dose levels of 100 or 200 ppm (estimated to be 14 and 29 mg/kg/day for 103 weeks. The control group consisted of 25/sex untreated mice. No data on systemic effects were presented. The study report mentions that body weight in females was possibly decreased in the later part of the study at both doses but males were not affected. TB-1 was not able to verify an effect on female body weight. **The LOEL for systemic effects is > 29 mg/kg/day.**

At the doses tested, there was no treatment-related increase in tumor incidence when compared to controls. Dosing was not considered adequate by TB-I based only on information in this study. However, the dose levels tested would be expected to cause significant inhibition of plasma ChE and RBC AChE to help justify adequacy of dosing.

This carcinogenicity study in the mouse is ACCEPTABLE and satisfies the guideline requirement for a carcinogenicity study (83-2(b)) in mice.

E. **Developmental toxicity.**

83-1a. Rat Study (1985).

Four groups of 27 assumed pregnant rats (Charles River Crl. COBS™ CD™ (SD)(BR)) were dosed as control, 10, 20 or 100 mg/kg/day on days 6 through 15 of gestation. Diazinon (purity not specified) was suspended in 0.2% carboxymethyl cellulose and the rats were dosed by gavage at a rate of 10 mL/kg/day. The rats were sacrificed on day 20 of gestation. MRID No.: 00153017.

At 100 mg/kg/day maternal body weight gain was decreased particularly during the 6-10 day interval (-11±2 gms vs +14±2 gms for the control). After that interval the rats showed recovery but net gain was 25% less for the high dose group at sacrifice. **The maternal toxicity LOEL is 100 mg/kg/day based on body weight gain decrease. The NOEL is 20 mg/kg/day.**

The mean fetal weight in the 100 mg/kg/day dose group was increased (~6%) and the mean number of live fetuses in this groups was slightly reduced. There were also noted slight increases in pre and postimplantation loss. An increase in rudimentary T-14 ribs that was within historical control range was also noted. Neither of these effects were considered sufficient to support a LOAEL. **The LOAEL for developmental toxicity is > 100 mg/kg/day the highest dose tested. The NOAEL is > 100 mg/kg/day.**

This study is classified ACCEPTABLE and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700 and 83-3a) in the rat.

83-1b. Rabbit Study (1981).

In a developmental toxicity study (MRID No.: 00079017) diazinon (89.2% purity suspended in 0.2% carboxymethyl cellulose) was administered by gavage (1 mL/kg) to four groups of assumed pregnant New Zealand White Rabbits at dose levels of 0 (vehicle control), 7, 25 or 100 mg/kg/day on days 6 to 18 of gestation.

At 100 mg/kg/day there were 9 deaths in the group of 22 does (40.9%). Clinical symptoms including tremors and convulsions and body weight gain decreases as well as gastro-intestinal hemorrhages and erosions were noted. **The LOAEL for maternal toxicity is 100 mg/kg/day based on deaths. The NOAEL for maternal toxicity is 25 mg/kg/day.**

No compound related effects on the fetuses were evident. **The LOAEL for developmental toxicity is > 100 mg/kg/day, the highest dose tested. The NOAEL for developmental toxicity is ≥ 100 mg/kg/day.**

This developmental toxicity study in rabbits is classified ACCEPTABLE (GUIDELINE) and satisfies the guideline requirement for a developmental toxicity (OPPTS 870-3700; §83-3b) in the rabbit.

F. **Reproductive toxicity (2-generation).**

83-4. Rat two-generation reproduction (1989.

In a multi generation reproduction study (MRID No.: 41158101), four groups of 30/sex Sprague-Dawley strain rats were dosed as control, 10, 100 or 500 ppm of diazinon (equivalent to 0, 0.67, 6.69 or 35.15 mg/kg/day in male, and 0, 0.77, 7.63 or 41.43 mg/kg/day in females) for 10 weeks and mated (1:1) to produce F1 litter pups. The F1 litters were culled and mated to produce the an F2 generation.

In the parental groups, at 100 ppm there was deceased weight gain (5-6% persistent for males in the second parental group and transitory for females.). At 500 ppm there were tremors in females; decreased male and female mating and fertility indices (second parental group) and increased gestation length. Dystocia and death were slightly increased but not definitely associated with treatment. **The LOEL is 100 ppm (6.69 mg/kg/day) based on decreased parental weight gain. The NOEL is 10 ppm (0.67 mg/kg/day).**

In the pups, at 100 ppm there was mortality and decreased weight gain during lactation. At 500 ppm there were decreases litter size and viable pups. **The LOEL is 100 ppm (6.69 mg/kg/day) based on pup mortality and decreased weight gain. The NOEL is 10 ppm (0.67 mg/kg/day).**

This study is classified as ACCEPTABLE and satisfies the requirement for a series 83-4 multi generation reproduction toxicity in rats.

G. **Neurotoxicity Testing.**

81-8. Acute neurotoxicity screen - rats (1994)

In an acute neurotoxicity screening study (MRID No.: 43132201 and 43132204), groups of 15/sex rats (Sprague-Dawley) were dosed as control 2.5, 150, 300 or 600 mg/kg of diazinon (D-Z-N technical 88% purity) in corn oil by gavage. 10/sex/group were assigned to the main phase of the study to assess for clinical signs, FOB and motor activity; the other five were assessed for ChE/AChE activity.

Plasma ChE was inhibited at all dose levels (27% for males and 47% for females in the 2.5 mg/kg dose group) and RBC AChE was inhibited at 150 mg/kg (83% for males and 76% for females) at the time of peak effect (about 9 hours postdosing). ChE was equivalent to the controls at day 15 but RBC AChE still remained inhibited for both males and females especially at the higher dose levels. Brain AChE was unaffected when assessed at day 15. **The LOEL for RBC AChE inhibition is 150 mg/kg**. **The NOEL for RBC AChE inhibition is 2.5 mg/kg. The LOEL for plasma ChE inhibition is < 2.5 mg/kg.**

Based on the FOB assessments, effects at 150 mg/kg included abnormal gait (3/10 males, 7/10 females), ataxic gait (3/10 females), decreased body temperature (-2.1%, females), decreased rearing counts (-33% females), stereotypy (3/10 females) and fecal consistency and stained fur (3/10 males). Numerous other FOB parameters were affected at 300 mg/kg and above, of these tremors (6/10 females and 5/10 males at 300 mg/kg) were noted and dehydration (6/10 females) were noted. Refer to DER for additional parameters affected. Motor activity was decreased for males (27%, not significant) and females (46% $p < 0.01$) at 150 mg/kg and above. Body weight gain in males was decreased in the 300 (25%) and 600 (29%) mg/kg dose groups. Deaths (2 males and 1 female) resulted at 600 mg/kg. No histopathological lesions attributed to treatment were indicated. **The LEL for neurotoxicity is 150 mg/kg based mainly on ataxic gait and supported by other effects believed to be related to ChE/ACHE inhibition. The NOEL for neurotoxicity is 2.5 mg/kg.**

This study is classified as MINIMUM. The study satisfies the requirement for a series 81-8ss acute neurotoxicity screen study. No additional series 81-8ss acute neurotoxicity study data are required at this time. The limiting factor considered in classifying this study as MINIMUM is that no NOEL was established for plasma ChE inhibition.

Special accompanying study especially designed to assess NOEL for ChE/AChE. HED Doc. # 011375.

Five groups of 15 Sprague-Dawley rats/sex were dosed as control, 2.5, 150, 300 or 600 mg/kg diazinon MG87% (D*Z*N, 88% purity) by gavage in corn oil and were sacrificed in groups of 5/sex after 3, 9 or 24 hours. These intervals were designated as pre-peak, peak and post-peak for effects. The rats were assessed for clinical signs and for plasma ChE, RBC and brain AChE. MRID No.: 43132203.

Clinical signs were first evident in the 300 mg/kg dose group males at 9 hours and at 600

mg/kg at 3 hours. Males were more frequently affected than females. Plasma ChE was inhibited at 2.5 mg/kg by 30% for males and 60% for females after 9 hours and to a lesser extent at the other intervals. 66-91% inhibition was noted for all other intervals at higher doses. RBC AChE was inhibited 40% ($p < 0.01$) in females dosed with 2.5 mg/kg and 42 to 82% at the higher doses for all other intervals. Four brain regions (cerebellum, cerebral cortex, striatum and hippocampus) and the spinal cord were also assessed. Definite brain AChE inhibition (31 to 68%) was noted at 150 mg/kg in all four regions and the spinal cord. Thus, the LEL for plasma ChE and RBC AChE is < 2.5 mg/kg for both sexes but the NOEL and LEL for brain AChE are 2.5 and 150 mg/kg. **Limited correlation between enzyme inhibition with symptoms was apparent since at 9 hours the symptoms were maximal and inhibition (> 77% in brain, >74% in RBC and >77% in plasma at 600 mg/kg) were reported but the enzymes remained inhibited when the symptoms regressed at 24 hours.**

This study is classified as Supplementary (study is a non-guideline study). This study, however, provides information complementary to the definitive series 81-8ss acute neurotoxicity study (MRID No.: 431322-04).

Second Special Study to assess for the cholinesterase NOAEL and LOAEL and neurotoxicity responses following acute administration.

EXECUTIVE SUMMARY:

In this 2 part study, the behavioral effects and potential for inhibition of ChE/AChE of Diazinon MG87% was assessed in Sprague-Dawley Crl:CD^{R}BR/VAF/Plus strain rats. MRID No.: 44219301.

In Part 1 (behavioral effects), four groups of 5 rats/sex were dosed with 0, 100, 250 or 500 mg/kg of diazinon (undiluted) and additional groups of females were dosed with 25 or 50 mg/kg and the rats observed for clinical signs for 14 days.

At 100 mg/kg, females were noted to have one incident of hypoactivity. At 250 and/or 500 mg/kg, miosis, hypoactivity, fur staining, and/or loss of pain reflex and at 500 mg/kg there was one death. These findings were corroborated by the ChE/AChE part of the study which also demonstrated miosis at 100 mg/kg in a single male rat. **The LOEL is 250 mg/kg based on miosis and hypoactivity. The NOEL is 100 mg/kg but this is considered a threshold dose level.**

In Part 2 (ChE/AChE effects), seven groups of males were dosed as control, 0.05, 0.5, 1, 10, 100 or 500 mg/kg and seven groups of females were dosed as control, 0.05, 0.12, 0.25, 2.5, 25 or 250 mg/kg and sacrificed ~24 hours later. Observations on their behavior reactions were noted and the blood and brain were assessed for ChE/AChE.

The precision of the ChE/AChE assays was considered fair to poor but not sufficiently poor to preclude an assessment of the potential for diazinon to inhibit ChE/AChE. Plasma ChE was inhibited at 2.5 mg/kg in females (61%) and at 10 mg/kg in males (44%). RBC AChE was inhibited at 25 mg/kg in females (35%) and at 100 mg/kg in males (49%). Brain AChE was inhibited at 25 mg/kg in females (36%, not significant) and at 250 mg/kg (70%) and at 500 mg/kg in males (69%). **The LOEL is 2.5 mg/kg based on 61% plasma ChE inhibition in females. The NOEL is 0.25 mg/kg.**

This special acute oral study is classified as ACCEPTABLE (Non-Guideline). This study does not satisfy the guideline requirement for an acute oral study (81-1) in the rat. This guideline requirement has been satisfied by other studies.

82-7 Subchronic Neurotoxicity - rat (1994).

In a subchronic neurotoxicity study (MRID No.: 43549302) 5 groups of 15/sex Sprague-Dawley Crl CD^R BR strain rats were dosed as controls, 0.3, 30, 300 or 3000 ppm corresponding to approximately 0.018, 1.8, 18 and 180 mg/kg/day of D*Z*N diazinon MG87% for 90 days with periodic assessments for clinical signs and FOB, motor activity and blood ChE/AChE. Regional brain AChE activity and neurohistopathology were assessed at termination.

Principal clinical signs included (muscle fasciculations, 8/15 females; hyper-responsiveness and tremors, decrease in grip strength: 15-20% in males and 14-39% in females); body weight and gain and food consumption decrease in both sexes were noted at 3000 ppm only. **The LOEL for systemic and neurotoxicity effects is 3000 ppm (180 mg/kg/day) based on weight gain decrease and signs of nervous system perturbation. NOEL is 300 ppm (18 mg/kg/day).**

At 30 ppm, plasma ChE (79%-86% in females, 37%-45% in males) and RBC AChE (53-60% in females and 37%-75% in males) and brain AChE cerebral cortex/hippocampus only (25% in females) were inhibited. Other regional brain AChE sources were inhibited at 300 ppm (55%-75% in females) but only at 3000 ppm in males 62% - 73%). Conclusions regarding inhibition of brain AChE are deferred to an accompanying study (MRID No. 43543901) which was especially designed to assess regional brain AChE inhibition. **The LOEL for plasma ChE and RBC AChE inhibition is 30 ppm and the NOEL is 0.3 ppm.**

This study is classified as ACCEPTABLE and together with an accompanying study (MRID NO.: 43543901) satisfy the requirement for a series 82-7 subchronic neurotoxicity screen study with rats.

Special study to assess for the NOEL and LOEL for ChE and AChE.

In a special study (MRID #43543901) designed to assess the time course for and regional brain inhibition of ChE/AChE, four groups of 15/sex Sprague-Dawley Crl CD^{R}BR strain rats were dosed as control, 0.3, 30, 300 or 3000 ppm of diazinon (D*Z*N MG87%) corresponding to approximately 0.02, 2.4, 23 and 213 mg/kg/day in their diets and 5/sex/group were sacrificed at weeks 1, 2 and 4 and plasma ChE and RBC and brain AChE assessments were made. The central nervous system was dissected into the cerebellum, hippo-campus, cerebrum, striatum and thoracic spinal cord in order to assess for potential differences in regional sensitivity.

Systemic effects including cumulative body weight gain decreases of 26% in males and 39% in females and decreased food consumption (21% in males and 27% in females) and muscle fasciculation (3 males and 8 females at day 8) were noted in the 3000 ppm dose group only. At 30 ppm plasma ChE (males 59% and females 81%) and RBC ACHE (39-58% males and 38-59% females) were inhibited. At 300 ppm brain AChE (62-72% at week 4 in females for all regions, only the cerebellum ~22% in males) was inhibited. Maximum inhibition of blood and brain ChE/AChE was attained at week 2 and essentially remained at that level by week 4 without

evidence of adaptation. There were no marked or consistent differences in sensitivity in brain regions to AChE inhibition (refer to DER for discussion). **The LOEL for plasma ChE and RBC AChE is 30 ppm and the NOEL is 0.3 ppm. The LOEL for brain AChE is 300 ppm and the NOEL is 30 ppm.**

This study is classified as SUPPLEMENTARY. The study was designed to complement a series 82-7 subchronic neurotoxicity study and provides data that establish the time course of plasma ChE and RBC and brain AChE. It is noted, however, that the data from these two studies must be considered against the entire data base for assigning the NOEL and LOEL for plasma ChE and RBC and brain AChE.

H. ***Mutagenicity (series 84-2).***

The following table summarizes the key studies used to support the mutagenicity/genetic toxicity testing requirements for diazinon. Only studies classified as ACCEPTABLE are included. Note the results comments entries were provided by Nancy McCarroll.

Study Identification	Results/Comments
Gene Mutation	
1. Salmonella typhimurium/ Escherichia coli. MRID No.: 41557404 HED Document No.: 010062	Independently performed tests were negative in S.typhimurium strains TA1535, TA1537, TA98 and TA 100 and E.Coli strains WP2 uvrA^{-} up to the highest dose tested (5000 μg/plate ± S9).
2. Mouse lymphoma L5178Y TK$^{\pm}$ for- ward gene mutation assay. MRID Nos.: 40660802 and 41119701 HED Document Nos.: 007059 and 007553	The test was negative up to the cytotoxic levels (120 μ/ML -S9 and 60 μg/mL +S9).
Chromosome Aberration	
Mouse micronucleus assay. MRID No.: 40660805 and 41603201 HED Document No.: 007229 and 010062	Negative in male and female CD-1 mice up to lethal doses administered by gavage (60 or 120 mg/kg). No evidence of cytotoxic effect on the target cells.
Other Mutagenic Mechanisms	
1. In vitro sister chromatid ex-change (SCE) in human lymphocytes. MRID No.: 41577301 HED Document No.: 010062 and 010722	Study was weakly positive showing reproducible but not dose-related significant increases in SCE frequency over an S9-activated concentrations range of 6.68-66.8 μg/mL. Higher levels (200 μg/mL +S9 or 66.8 μg/mL - S9) were cytotoxic.
2. In vivo SCE male ICR mice MRID No.: 41687701 HED Document No.: 009619	The test was negative at oral doses of 10-100 mg/kg. Overt toxicity and bone marrow cytotoxicity were apparent in the treated males at the highest dose tested.
3. In vivo SCE in female CD-1 strain mice. MRID No.: 43060601 HED Document No.: 010945	The test was negative in female mice at oral doses of 150-175 mg/kg. Overt toxicity and bone marrow cytotoxicity were apparent in the treated females at concentrations 150 mg/kg.
4. Primary rat hepatocyte un-scheduled DNA synthesis. MRID No.: 41557405 HED Document No.: 010062	Independently performed tests were negative up the highest dose tested (120 μg/mL). Higher levels (163.1 μg/mL) were insoluble.

I. ***Metabolism.***

The series 85-1 general metabolism requirement is considered satisfied by a 1989 study (MRID No.: 41108901, HED Document No.: 010338). In this study a series of experiments were run with ^{14}C labeled diazinon in Sprague-Dawley strain rats. After 24 hours most of the ^{14}C

was recovered in the urine (58.2% ♀ and up to 93.3% ♂) and smaller amounts (<2.5%) in the feces. After 7 days recovery was 96.7% to 100.25% and < 1% of the label remained in the tissues. The highest level was in the blood. Three major metabolites were identified in the urine to indicate that diazinon is metabolized to liberate the pyrimidinyl group that is oxidized and excreted. Only trace amounts of parent diazinon were present in the urine or feces. Refer to DER for chemical identification of the metabolites.

J. **Dermal Absorption/Penetration.**

There is no acceptable series 85-2 (or 870.7600) dermal absorption/penetration study available for diazinon. A dermal absorption/penetration study (MRID No.: 44982801) with human volunteers was submitted and it was determined that the data should not be used for human health risk assessment. The HIARC (September 21, 1999, HED Doc. No.: 013745) determined that a dermal absorption rate of 100% should be used for risk assessments. The TESC determined a 100% dermal absorption factor based on the similarity of results (mortality) observed at the same dose (100 mg/kg/day) via the oral (in the developmental toxicity study) and dermal (21-day dermal) routes in the same species (rabbits) thus indicating that an assumption of 100% absorption to be appropriate.

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